

Early Development and Durability of SARS-CoV-2 Antibodies Among Solid Organ Transplant

Recipients: A Pilot Study

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Keywords: transplantation, COVID-19, SARS-CoV-2, antibodies

Running title: SARS-CoV-2 antibodies among transplant recipients

Word count: 498

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DISCLOSURE

The authors of this manuscript have no conflicts of interest to disclose as described by *Transplantation*.

ABBREVIATIONS

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

SOTR: solid organ transplant recipient

COVID-19: Coronavirus disease 2019

ELISA: enzyme-linked immunosorbent assay

IVIg: intravenous immunoglobulin

MMF: mycophenolate mofetil

CCP: COVID-19 convalescent plasma

AMR: antibody mediated rejection

FSGS: focal segmental glomerulosclerosis

N: nucleocapsid

anti-S1-IgG: IgG antibodies to spike protein

The immune response to SARS-CoV-2 may be blunted in immunosuppressed individuals, impacting reinfection risk, treatment selection, and vaccine protocols. In this small pilot study, we quantified early antibody response and durability after COVID-19 in solid organ transplant recipients (SOTRs).

SOTRs with PCR-confirmed COVID-19 were recruited through the electronic medical record August 21-October 15, 2020. Participants underwent at-home blood sampling with the TAP™ Blood Collection Device, Second Edition (7SBio, Medford, MA). Serum samples were screened using Elecsys® anti-SARS-CoV-2 immunoassay (Roche), which uses a recombinant protein representing the nucleocapsid (N) antigen. Confirmatory testing was performed using EUROIMMUN anti-SARS-CoV-2 enzyme-linked immuosorbent assay (ELISA) for semi-quantitative detection of IgG antibodies to spike protein (anti-S1-IgG), a likely correlate of neutralizing immunity.¹ This study was approved by the Institutional Review Board at the Johns Hopkins School of Medicine.

Eighteen SOTRs were studied (9 kidney; 5 liver; 1 kidney/liver; 2 lung; 1 composite tissue allograft), for whom COVID-19 occurred at a median of 6 years (IQR 2-9) post-transplant. Median age was 56 years (IQR 42-63); 56% were female; 33% were Black and 11% were Hispanic. Maintenance immunosuppression included low-dose prednisone (67%), tacrolimus (94%), mycophenolate mofetil (MMF) (66%), and sirolimus (6%). MMF was held in 92% of participants prescribed MMF at the time of diagnosis, and subsequently restarted in 45%. Two recipients were receiving IVIg at the time of diagnosis, 1 kidney recipient for focal segmental glomerulosclerosis and 1 lung recipient for chronic antibody mediated rejection. Most participants (89%) had experienced COVID-19 symptoms; 72% were hospitalized. Among those hospitalized, 15% were admitted to the ICU and 8% were mechanically ventilated. COVID-19 convalescent plasma (CCP) was administered to 3 kidney and 2 lung recipients.

At median 98 days (IQR 55-147) after COVID-19 diagnosis, 78% had reactive screening immunoassays (100% among those who were not hospitalized, and 69% among those who were hospitalized) (Table 1). Of the four patients with non-reactive immunoassays, 2 were the lung recipients treated with CCP and 1 was the kidney recipient receiving IVIg.

Of those who screened positive by immunoassay, anti-S1-IgG was detectable by ELISA in 83% (75% among those who were not hospitalized, and 88% among those who were hospitalized). SOTRs who received CCP and/or IVIg were less likely to develop anti-S1-IgG and had lower antibody levels.

In this study of antibody development among immunosuppressed SOTRs, we found antibody levels suggestive of neutralizing immunity in the majority of participants. However, those who were administered CCP and/or IVIg were less likely to mount a durable immune response. This raises the possibility that exogenous antibody preparations may blunt durable antibody formation, although the cohort size is too small to make robust conclusions.² Larger studies are needed to evaluate these differences.

Interestingly, among those who had more severe disease, there was a trend towards higher antibody levels. Seropositivity might decline over time;³ however, we were unable to distinguish between impaired production or rapid decrement. Strengths of this study include antibody quantification, longer follow-up time than previously published series,⁴ and a diverse group of SOTRs. Limitations include a relatively small sample size precluding subgroup analysis by level of maintenance immunosuppression, lack of serial time points, and inability to rule out occult hypogammaglobulinemia.

In conclusion, we observed that SOTRs could mount a durable immune response to SARS-CoV-2, however passive immunity may diminish the natural immune response.

Table 1. Seropositivity, Hospitalization, and Mean Signal-to-Threshold Values of Anti-SARS-CoV-2 Antibodies Among Solid Organ Transplant Recipients with Prior COVID-19.

	Overall (n=18)	Outpatient (n=5)	Hospitalized (n=13)	
			No CCP or IVIg (n=7)	CCP or IVIg (n=6)
Total reactive anti-SARS-CoV-2 antibody by screening Immunoassay, n (%)	14/18 (78)	5/5 (100)	6/7 (86)	3/6 (50)
Total reactive anti-S1-IgG by ELISA, n (%)	10/12 (83)	3/4 (75)	5/6 (83)	2/2 (100)
Signal-to-threshold value, mean (median) (Arbitrary Unit ratio)*	5.9 (5.2)	4.4 (5.0)	7.5 (7.7)	3.9 (3.9)
Days since COVID-19 diagnosis, median (IQR)	98 (55-147)	141 (106-147)	129 (67-166)	51 (3-65)

Abbreviations: ELISA, enzyme-linked immunosorbent assay; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SOTR, solid organ transplant recipient

*Optical density of the sample about the threshold at serum dilution of 1:101 divided by calibrator provided arbitrary unit ratio (A.U.) for which ≥ 1.1 was considered positive and ≥ 0.8 were considered indeterminate.

ACKNOWLEDGEMENTS

This research was made possible with generous support of the Ben-Dov family. This work was supported by grant number F32DK124941 (Boyarsky), K01DK101677 (Massie), and K23DK115908 (Garonzik-Wang) from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), K24AI144954 (Segev) from National Institute of Allergy and Infectious Diseases (NIAID), and by a grant from the Transplantation and Immunology Research Network of the American Society of Transplantation (Werbel). The analyses described here are the responsibility of the authors alone and do not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products or organizations imply endorsement by the US Government.

We also acknowledge the following individuals for their assistance with this study: Oliver B.

Laeyendecker PhD; Yukari C. Manabe, Christine M. Durand MD, Allan Massie PhD, Teresa Po-Yu Chiang MD MPH, Alexandra T. Strauss MD, Amber B. Kernodle MD MPH, Kayleigh M. Herrick-Reynolds, MD, Mackenzie A. Eagleson MD, Andrew M. Hallett MD, Victoria A. Bendersky, MD, Richard Wang BA, Jake A. Ruddy BS, Leyla R. Herbst BA, Michelle R. Krach MS, Ross S. Greenberg BA, Marie S. Nunez Duarte BA

REFERENCES

1. Klein SL, Pekosz A, Park HS, et al. Sex, age, and hospitalization drive antibody responses in a COVID-19 convalescent plasma donor population. *J Clin Invest.* 2020.
2. Roback JD, Guarner J. Convalescent Plasma to Treat COVID-19: Possibilities and Challenges. *JAMA.* 2020;323(16): 1561-1562.
3. Patel MM, Thornburg NJ, Stubblefield WB, et al. Change in Antibodies to SARS-CoV-2 Over 60 Days Among Health Care Personnel in Nashville, Tennessee. *JAMA.* 2020;324(17): 1781-1782.
4. Caillard S, Benotmane I, Gautier Vargas G, Perrin P, Fafi-Kremer S. SARS-CoV-2 viral dynamics in immunocompromised patients. *Am J Transplant.* 2020.

